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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,324	12/15/2001	Christopher Thomas Walsh	55046 (70207)	8192
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EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			EXAMINER KERR, KATHLEEN M	
			ART UNIT	PAPER NUMBER

1652

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/017,324

Applicant(s)

WALSH ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 October 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-53 and 55-59 is/are pending in the application.
- 4a) Of the above claim(s) 56-58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-53, 55 and 59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (mailed on January 30, 2004), Applicants filed a response and amendment received on July 6, 2004 and October 7, 2004. Said amendment cancelled Claim 54 and amended Claims 1, 12, 14, 18, 22, 28, 31, 33, 34, 47, 48, and 59. Thus, Claims 1-53 and 55-59 are pending in the instant Office action.

Election

2. Claims 56-58 remain withdrawn from consideration as non-elected inventions. Claims 1-53, 55, and 59 will be examined herein.

This application contains Claims 56-58 drawn to an invention nonelected; said claims are not subject to rejoinder since method claims have been elected. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 C.F.R. § 1.144) See M.P.E.P. § 821.01.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/256,596 and 60/332,763 filed on December 18, 2000 and November 6, 2001, respectively.

Withdrawn - Objections to the Specification

4. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicant's amendment.

5. Previous objection to the specification for a typographical error on page 45 is withdrawn by virtue of Applicant's amendment.

6. Previous objection to the specification (page 45, describing Figure 3c) is withdrawn by virtue of the Examiner's reconsideration. Applicant's clarification is wholly inadequate. The Examiner asked how dimerization occurs in the absence of a PCP domain (the dimerization domain, see Figure 3b) wherein the "in vitro" reaction (that in solution in the absence of the PCP domain, see Figure 3c) contains no PCP domain or an analogous protein. Applicant's response was "One reading the description of Figure 3c in context would understand the role of the PCP domain, especially when read in light of Figure 3b, which immediately precedes it." Clearly, this is wholly not the case since, as noted by the Examiner; it is exactly the contrast to Figure 3b that renders the "in vitro" experiment confusing. The Examiner will assume that the dimerization occurs in the "in vitro" experiment (i.e., not using the PCP domain) due to high concentration of reactants in solution.

7. Previous objection to the specification for the description of compounds 22-26 is withdrawn by virtue of Applicant's amendment as well as the Examiner's reconsideration. The amendment of "data not shown" answers the Examiner's question as to whether these compounds were actually practiced in methods. However, the question of what TE domain was used would still be at issue. Applicant comments that the Tyr TE domain as used in Example 3 was used; this is consistent with the mention of "compound 22, an analog of Example 3" (see page 46), etc. Apparently, this improper grammar indicates that compound 22 was used in an example analogous to Example 3. This is sufficient to obviate the rejection.

Withdrawn - Objections to the Claims

8. Previous objection to Claim 48 for containing a typographical error in claim dependence is withdrawn by virtue of Applicant's amendment.

9. Previous objection to Claim 54 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicant's cancellation of said claim.

New or Maintained - Objections to the Claims

10. Previous objection to Claim 18 for containing informalities is maintained. Applicant's amendment still includes a period after "stereoconfiguration", which period should be deleted letting the comma link the preceding portion of the claim to the following wherein clause. Correction is required.

11. Claims 28-33 are objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from two claims at the same time (not in the alternative) as found in Claim 28. See M.P.E.P. § 608.01(n).

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

12. Previous rejection of Claims 1-55 and 59 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "TE" is withdrawn by virtue of Applicant's amendment.

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13. Previous rejection of Claims 18-27, 47-48, and 50-55 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitations of R_1 and R_2 is withdrawn by virtue of Applicant's amendment.

14. Previous rejection of Claims 28-33 under 35 U.S.C. § 112, second paragraph, as being indefinite for the definition of R_1 and R_2 is withdrawn by virtue of Applicant's amendment.

15. Previous rejection of Claims 31 and 33 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "and the like" is withdrawn by virtue of Applicant's amendment.

16. Previous rejection of Claim 33 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitation of the spacer being non-peptidic when glycine is in the Markush group is withdrawn by virtue of Applicant's arguments.

17. Previous rejection of Claims 34-55 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "essentially" is withdrawn by virtue of Applicant's amendment removing the term.

18. Previous rejection of Claims 34-55 under 35 U.S.C. § 112, second paragraph, as being indefinite for the "contacting" step is withdrawn by virtue of the Examiner's reconsideration in light of Applicant's arguments.

19. Previous rejection of Claim 59 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitation that "can be" is withdrawn by virtue of Applicant's amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

20. Previous rejection of Claims 4 and 37 under 35 U.S.C. § 112, second paragraph, as being indefinite for the relative term “weakly-nucleophilic” is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant argues that because the term is found in other claims in other patents, the term is automatically clear as used in the instant claims; this is not the case. As previously noted, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Thus, the instant rejection is maintained.

21. Previous rejection of Claims 6-8 and 39-41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitations of the pH is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the Federal Circuit notes that “about” is not a precise term as is based on the facts of the case. The Examiner does not disagree. As noted previously, the facts of the application give no indication as to the breadth of the term. Applicant also argues that the District Courts around the U.S. are “inclined to uphold” the use of the term “about”. The Examiner has not demanded that Applicant not use the term - only that the term be clear. In Applicant’s arguments about the District of Massachusetts, data with error gives the imprecise term “about” clarity. That is not the case in the instant application wherein no error on pH ranges is described. For all these reasons, the instant rejection is maintained herein.

22. Previous rejection of Claims 10, 12-33, and 59 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “hydrocarbon” in Claims 10, 12, 18, and 59 is maintained.

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Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the term "hydrocarbon group" as used in the claims and as defined on page 16 of the specification is distinct from the well-known term "hydrocarbon" as whose definition was presented by the Examiner attached to the previous Office action. The Examiner fails to see this distinction and no evidence has been offered to set such a distinction forth. Thus, the instant rejection is maintained.

23. Previous rejection of Claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that the term "thioester" was a typographical error in the claim; however, the claim as posed on October 7, 2004 is not listed as "amended", despite what appears to be a stray mark over ---thio--- in thioester. Thus, the claim still reads "thioester" and the rejection is maintained.

24. Previous rejection of Claims 10, 28-33 and 54 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitations of the LINKER, the R group, z, and the sum of " $z+3m+3n$ " using the phrases like "about 4 carbon atoms" and "about 10 heteroatoms" is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that, like the term "about" with respect to pH above, the term "about" as used herein is not "fatally ambiguous". The Examiner disagrees that the term was categorized as such. In the previous rejection, the Examiner clearly notes, "the specification is replete with examples of *highly varied* substrates with various numbers of carbon atoms" (emphasis added). However, the variation at particular locations of this broad description of a

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linker is not indicated by these varied substrates. Thus, the specification does not aid in the interpretation of the term “about” as it applies in Claims 10 and 28, and clarification is required.

25. Previous rejection of Claims 12-33 under 35 U.S.C. § 112, second paragraph, as being indefinite for the compound “N-C₂-C₆alkanoylC₂-C₆aminoalkyl” is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant argues as follows:

“The language ‘optionally substituted C₁₋₁₂alkyl group’ is sufficiently broad to encompass compounds in which R is ‘N-C₂-C₆alkanoylC₂-C₆aminoalkyl group’. That is, the N-C₂-C₆alkanoylC₂-C₆aminoalkyl group is a C₂₋₆alkyl group substituted at the ω carbon (i.e., the terminal methyl carbon) with a carboxamide residue such as a C₁₋₅alkyl-C(O)NH group. However, in the interest of advancing prosecution, claim 12 has been amended to provide that R is optionally substituted C₁₋₁₂alkyl N-C₂-C₆alkanoylC₂-C₆aminoalkyl.”

Thanks to Applicant’s explanation to clarify how N-C₂-C₆alkanoylC₂-C₆aminoalkyl group is within the genus of optionally substituted C₁₋₁₂alkyl; however, the Examiner fails to see how the N-C₂-C₆alkanoylC₂-C₆aminoalkyl group is clear from the art. It is wholly unclear how a carboxamide group at the end of a compound can be signified by an “N” at the beginning of the name.

26. Previous rejection of Claims 20 and 48 under 35 U.S.C. § 112, second paragraph, as being indefinite for the limitations of the pH of the side chain is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant argues when considering the specification as a whole, the term “about” as it refers to the pH of side chains is clear. The Examiner is confused as to how one of skill in the art could ascertain the metes and

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bounds of the term since, as previously noted, the specification gives **no** indication of scope since pH values for side chains is not mentioned in the experiments so one of skill in the art would have to assume any side chain and, thus, any pH value from glutamate (acidic) to asparagine (basic) and then some considering non-native amino acid side chains. Thus, the ordinarily skilled artisan cannot ascertain the scope of the claims from any variability in the examples. The metes and bounds are not clear in the claims, and the specification does not aid in the interpretation of the term “about”. Clarification is required.

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

27. Previous rejection of Claims 1-55 and 59 under 35 U.S.C. 112, first paragraph, written description, is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that from pages 6-9 the specification gives “examples of substrates ... that fully enable and are commensurate with the scope of the claims.” This is not convincing because the rejection at hand is one of written description, not enablement. The substrates used in the claimed methods must have adequate written description for the claimed genus. As previously noted,

“To fully describe a genus, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.”

The claimed methods require the substrate used in the contacting step to produce a macrocyclic product, thus be functioning in the claimed methods. No correlation between structure and function of the enormous genus of any compound having a nucleophile and an

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activated acyl residue, as prescribed by the claim limitations of Claim 1, is described so that one of skill in the art could predict the structure of the substrates to be used in the claimed invention. Thus, the substrates to be used in the claimed methods lack adequate written description.

28. Previous rejection of Claims 34-55 under 35 U.S.C. § 112, first paragraph, written description, for not describing a single representative species is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that on pages 11-12, dimerization of a pentapeptide to form a decapeptide, which can then be cyclized, supports the claimed invention. The Examiner disagrees. The iteration step in Claim 34 requires more. In Applicant's example, the pentapeptide is elongated in the first step ("elongating a substrate which can not be cyclized") wherein the decapeptide is produced. No "repeating the elongation step" is performed. Thus, the instant claims lack even one representative species.

29. Previous rejection of Claims 1-55 and 59 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using NRPS TE domains with particular substrates, does not reasonably provide enablement for methods using any PKS TE domains with any substrate or methods using NRPS TE domains with any substrate is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues "Applicants [sic] specification is clearly enabled for the scope of the claims by disclosing multiple examples of TE domains appropriate to catalyze the macrocyclization reactions." The Examiner wholly disagrees with this statement. As previously

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stated on the record, no examples of functional, excised TE domains from PKSs are disclosed and only two examples of functional excised TE domains from NRPSs are disclosed.

Applicant continues "As the specification states at the top of page 8, substrate specificity of other excised TE domains can be determined by those skilled in the art by routine procedures." The Examiner wholly disagrees with this statement. As iterated separately for both PKS TE domains and NRPS TE domains with the broad genus of substrates, substrate specificity of TE domains would not be routine. As previously noted by the Examiner:

"The specification describes how excised TE domain a polyketide synthase, DEBS, **does not promote cyclization** (see specification page 3). No guidance is presented for the use of PKS TE domains, in particular for the substrates necessary for the use of PKS TE domains. The state of the prior art contradicts the claim that excised PKS TE domains promote cyclization. Thus, the predictability of using any substrate with an excised PKS TE domain is extremely low. For all these reasons, the instant claims are not enabled for using PKS TE domains." (emphasis added)

Thus, using excised PKS TE domains in the claimed methods is wholly not routine.

Moreover, for using excised NRPS TE domains, the Examiner previously noted:

"In the instant specification, all examples except one utilize the excised TE domain protein from the tyrocidine NRPS (TycC); a single example using the excised TE domain protein from the surfactin synthetase is also described. The examples using TycC somewhat systematically utilize substrates varied on the particular *peptide* theme of substrates to determine where the substrate can be flexible and where it cannot. In the case of TycC, this is described as a straightforward process; however, this process using other excised TE NRPS domain proteins is wholly unpredictable since all NRPS substrates are distinct, except for their peptide nature. And the substrates usable in the claimed methods do not require any such peptide nature! Moreover, in some claims, the length of the substrates is infinite (see Claim 10, wherein the linker comprises **at least** 14 atoms). The nature of the art, in the absence of crystallography data on the TE domain protein used in the methods, is directed trial-and-error at best to identify suitable substrates. To produce TE domain proteins that cyclize all the substrates in the claimed genus (or at least a significant number of them to include as few inoperative embodiments as possible) would require mutation of the proteins, which experimentation is wholly undescribed and unpredictable based on the instant disclosure. For all above reasons, the instant claims are not enabled to the full extent of their scope."

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Thus, the Examiner has clearly set forth the use of excised PKS TE domains as not routine having contrary information disclosed in the specification and for the reasons cited above. Moreover, the Examiner has also clearly set forth that the breadth of using excised NRPS TE domains with the entire genus of substrates is not routine since the breadth encompasses much more than mere screening as Applicant's would argue. For all these reasons, the instant rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 102

30. Previous rejection of Claims 1-8 and 11 under 35 U.S.C. § 102(a) as being anticipated by Trauger *et al.* is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. The declaration filed on July 6, 2004 under 37 C.F.R. § 1.131 has been considered but is ineffective to overcome the Trauger *et al.* reference. The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Trauger *et al.* reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The declaration filed references "Exhibit 1" as evidence; however, no such exhibit has been received. Such evidence is required, see 37 C.F.R. § 1.131(b).

Examiner's Note

31. At the end of Applicant's remarks, Dr. Patton's registration number is incorrect. The correct number is 50,373 according to Office records.

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Conclusion

32. Claims 1-53, 55, and 59 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

January 8, 2005